ARO 14618.1-C

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Stereochemistry of Reactions Involving

Cyclic Peroxides.

Final Report

LEVEL II

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25 September 1981

U.S. Army Research Office

Proposal #15618-C

Duke University

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REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER	2. GOVT ACCESSION NO. AD-A105999	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) Stereochemistry of Reactions Involving Cyclic Peroxides		5. TYPE OF REPORT & PERIOD COVERED Final Report 1 May 1978–30 April 81
		6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s) Ned A. Porter		8. CONTRACT OR GRANT NUMBER(s) NSF CHE 77-26088 ARO Proposal 15618-C
9. PERFORMING ORGANIZATION NAME AND ADDRESS Duke University Durham NC		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS
11. CONTROLLING OFFICE NAME AND ADDRESS U. S. Army Research Office Post Office Box 12211 Research Triangle Park, NC 27709		12. REPORT DATE 25 September 81
		13. NUMBER OF PAGES
14. MONITORING AGENCY NAME & ADDRESS(If different from Controlling Office)		15. SECURITY CLASS. (of this report) Unclassified
		15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)

Approved for public release; distribution unlimited.

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

NA

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

Autoxidation, cyclic peroxides, polymer degradation, food spoilage

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)
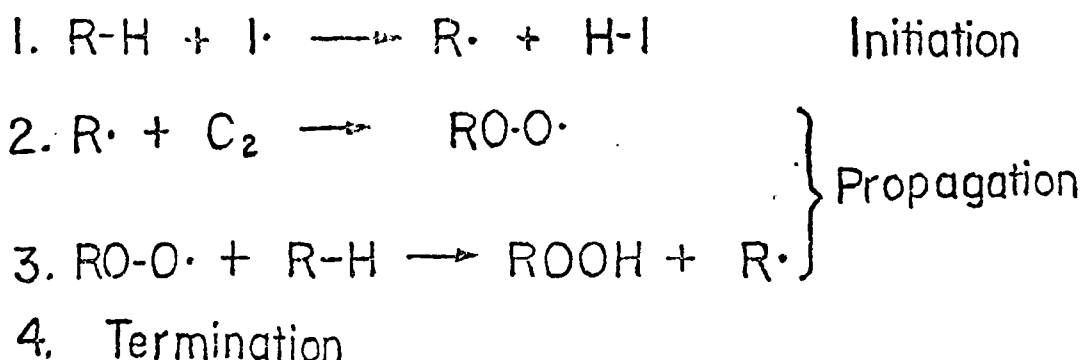
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20. Abstract

Several aspects of chemistry related to autoxidation, peroxy free radicals, and peroxides have been explored. Methods for preparation of complex unsaturated hydroperoxides have been developed and peroxy radicals derived from these hydroperoxies were studied as models for polyunsaturated fatty acid and polyolefin (i.e., polybutadiene and polyisoprene) autoxidation. We have established that peroxy radical cyclization and bicyclization occurs in models of polyunsaturated fatty acid oxidation and a new type of cyclization, serial cyclization, has been observed in polybutadiene oxidation models. Kinetic and stereochemical aspects of these cyclization reactions have been explored. The free radical oxidation of polyunsaturated fatty acids has been studied mechanistically. In particular, we believe that the H atom donating ability of the medium in which oxidation occurs is an important factor in determining the partitioning of peroxy free radicals between competitive pathways (i.e., β scission and cyclization). The results of these studies provide a firm basis for understanding the degradation of materials, foodstuffs, etc.

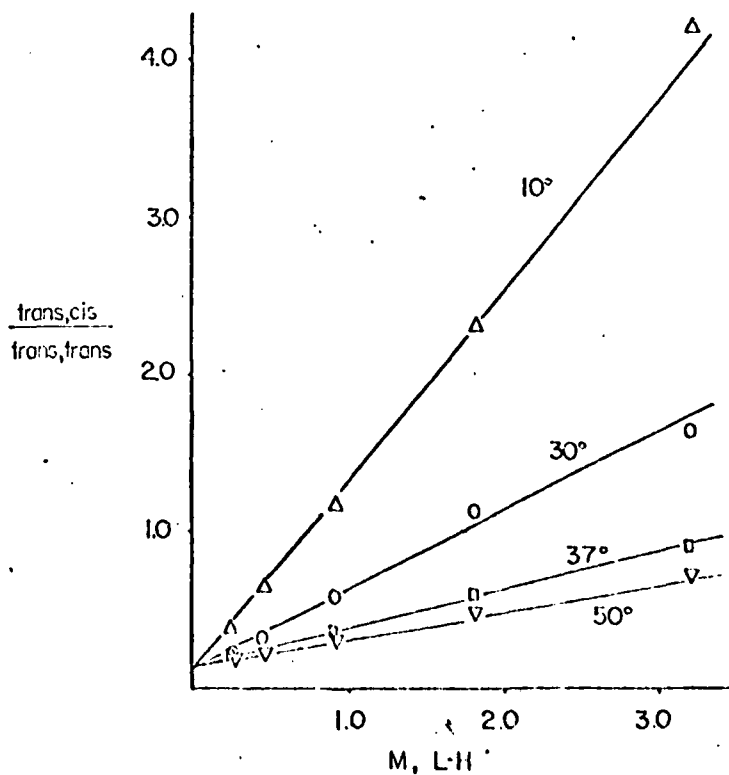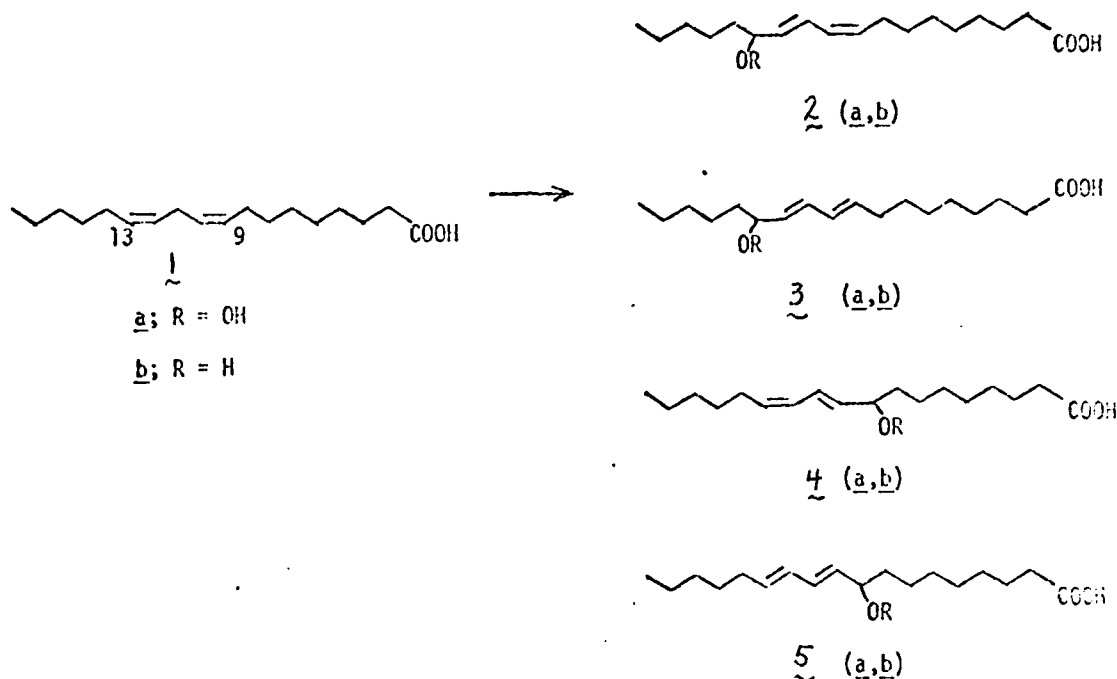| Accession For	
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a.) Statement of Problem Studied

The destruction of organic substrates by molecular oxygen is perhaps one of the most important organic reactions. Natural and synthetic polymers, biological materials such as lipids, and for that matter, any organic molecule exposed to the atmosphere may react with ground state molecular oxygen. It is no surprise then, that extensive investigations have focused on the kinetics of organic substrate oxidation by O_2. The "hydroperoxide mechanism" for autoxidation which is now generally accepted is outlined below.

$$1.\ R\text{-}H + I\cdot \longrightarrow R\cdot + H\text{-}I \qquad \text{Initiation}$$

$$2.\ R\cdot + C_2 \longrightarrow RO\text{-}O\cdot \quad \left.\right\}$$

$$3.\ RO\text{-}O\cdot + R\text{-}H \longrightarrow ROOH + R\cdot \left.\right\} \text{Propagation}$$

$$4.\ \text{Termination}$$

Despite the numerous studies on autoxidation and inhibition, surprisingly little research has been directed towards product study in autoxidation. It is true that for simple molecules like isopropylbenzene the primary autoxidation product is the tertiary hydroperoxide. However, if the organic substrate has several centers of unsaturation, the simple hydroperoxide product may not be found and in its place, cyclic peroxides are formed. For example, squalene absorbs two moles of oxygen upon autoxidation and one of these oxygen molecules is incorporated as a peroxide, rather than a hydroperoxide group. Although no rigorous structure proof was offered for the squalene oxidation product, it seems likely on the basis of subsequent work that the principal product of squalene autoxidation is one of the cyclic peroxides (1 or 2) formed by the mechanism described below:
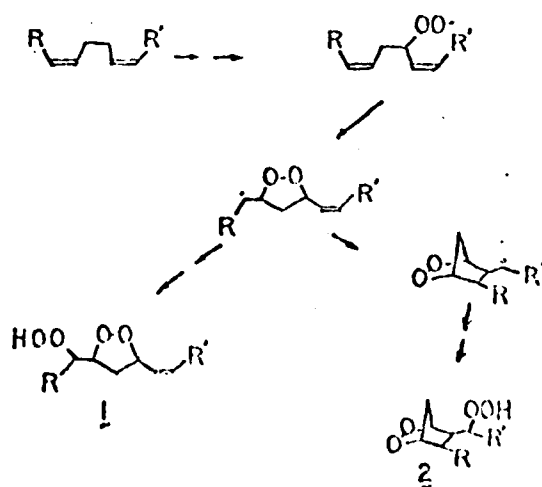
For some six years we have been involved in studies related to the mechanism of autoxidation and the synthesis of biologicaly important peroxides. These studies have resuled in the first syntheses of the important biological compound PGH$_2$ and PGG$_2$ and have provided mechanistic information about autoxidaticn of fatty acids, phospholipids, and polymer models. In this final report, two aspects of these studies are discussed, namely, (1) a unified mechanism for lipid autoxidation, and (2) a description of the stereochemical requirements of the S$_H$2 reaction.

$\underset{\sim}{2}$ (a̲,b̲)

$\underset{\sim}{3}$ (a̲,b̲)

$\underset{\sim}{4}$ (a̲,b̲)

$\underset{\sim}{5}$ (a̲,b̲)

$\underset{\sim}{1}$

a̲; R = OH

b̲; R = H

$\dfrac{trans,cis}{trans,trans}$

M, L·H

b.) Summary of the Most Important Results

1) Reversibility of Oxygen Entrapment in Autoxidation:

In the autoxidation of linoleic acid, both trans,cis and trans,trans hydroperoxides are formed. Thus, linoleic acid, 1, leads to four different hydroperoxides, 2a-5a. Two of these, 2a and 4a have the trans,cis geometry while 3a and 5a are trans,trans diene isomers. We have recently published a study of factors controlling the product distribution of 2-5. We find, in short, that the ratio of trans,cis/trans,trans products (2+4/3+5) formed during the initial stages (<2%) of oxidation is dependent on temperature and the concentration of linoleic acid. This ratio (2+4/3+5) varies from 4.2 (neat linoleic acid oxidations at 10°C) to 0.23 (0.24 linoleic acid in benzene at 50°C). The trans,cis/trans,trans ratio is presented in Figure 2 as a function of [L-H] (the concentration of linoleic acid in the oxidation) and temperature. Appropriate controls have been run to insure that the product ratios observed are independent of extent of oxidation (within the 2% oxidation range) and O_2 pressure.

The essential competition that accounts for the observed trans,cis/trans,trans ratio is β scission at peroxy radical conformer 7 (leading ultimately to a trans,trans product) vs. H atom abstraction by radical conformer pair 6/7 to give the trans,cis product.
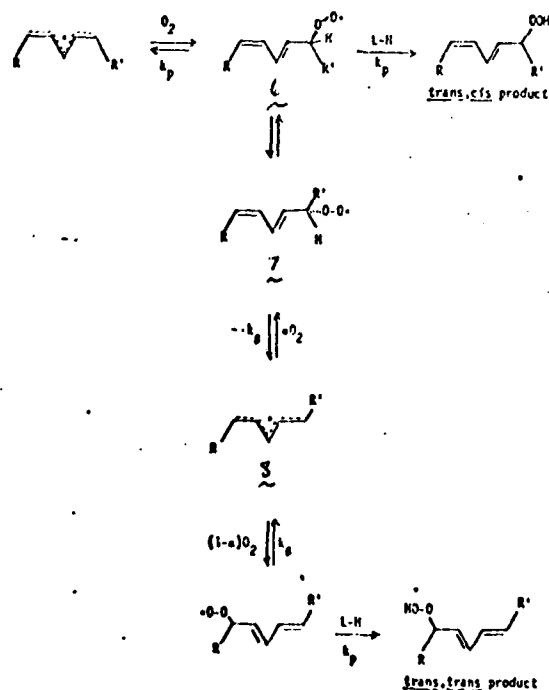
A kinetic derivation describing this system gives:

$$\frac{\text{trans,cis}}{\text{trans,trans}} = \frac{k_p[L-H]}{k_\beta(1-\alpha)} + \frac{\alpha}{(1-\alpha)}$$

Eq. 1

That is, the product ratio depends on [L-H] as is observed in Figure 2 and the valuable kinetic parameters k_β and α can be extracted from the data. (α is the partition factor of radical 8 between the trans,cis and trans,trans manifold.) Further, estimates of $\Delta H^{\neq}_\beta$, the enthalpy of the β scission process, can be obtained from temperature dependence data and $\Delta H^{\neq}_\beta$ is calculated to be in the 16-18 kcal/mole range. We should note that Benson had proposed in a classic paper that peroxy radical β scission is an important reaction in autoxidation. We have simply shown that this β scission process has a profound influence on product stereochemistry. We should also note that linoleic acid is the only good H atom dnor available in this autoxidation system but in reality $k_p[L-H]$ in Eq. 1 should be replaced by a summation term that includes all H atom donors,

$$\sum_{n=1}^{i} k_p^n [R_n-H] = KP.$$

We have chosen to define this important parameter as KP and it represents the total H atom donating ability of the medium of autoxidation.

2) Stereochemistry of the $S_H i$ Reaction on Peroxide

Little is known about the stereochemical requirements of the $S_H 2$ reaction. An $S_N 2$ type transitin state has been proposed and strong evidence has been presented that suggests that halogen atom attack on cyclopropane carbon occurs with stereochemical inversion. The $S_H 2$ reaction is apparently extremely sensitive to steric hindrance, and attack on carbon is limited to the strained cyclopropane series. Radical attack on heteroatoms such as O, N, or S is a much more common event, possibly because the steric hindrance of attack is much less for these di- and tri-valent atoms than it is for substitution at tetravalent carbon. Skell

-6-

suggests that "perhaps this type of displacement" (inversion) "will be found to be important for an unhindered substrate".
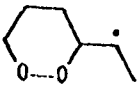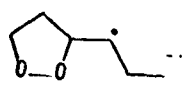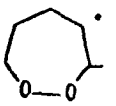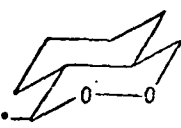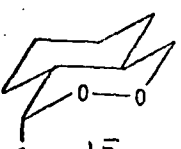
The S_Hi reaction reported here (Scheme 1) offers the possibility of studying the geometric requirements of S_H2 attack on the peroxide linkage since the attacking radical center and the peroxide bond are geometrically fixed by the cyclic peroxide molecular frame. We suggest that the critical geometric parameter for the S_Hi reaction is the dihedral angle, ϕ, about the O-C bond between the attacking radical and the leaving oxygen. Further, we propose that for maximum reactivity, this dihedral angle must be 180°. Our evidence in support of this hypothesis has been published in two recent papers, the results of which are summarized here.
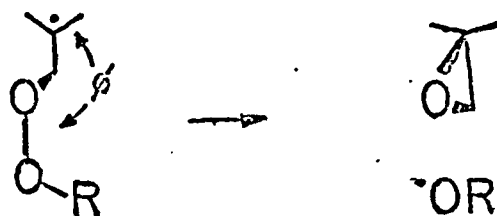
A series of β-bromo peroxides were reacted with Bu_3Sn-H affording the corresponding alkyl radicals. As an example, the bromide 9 was shown to react as follows:
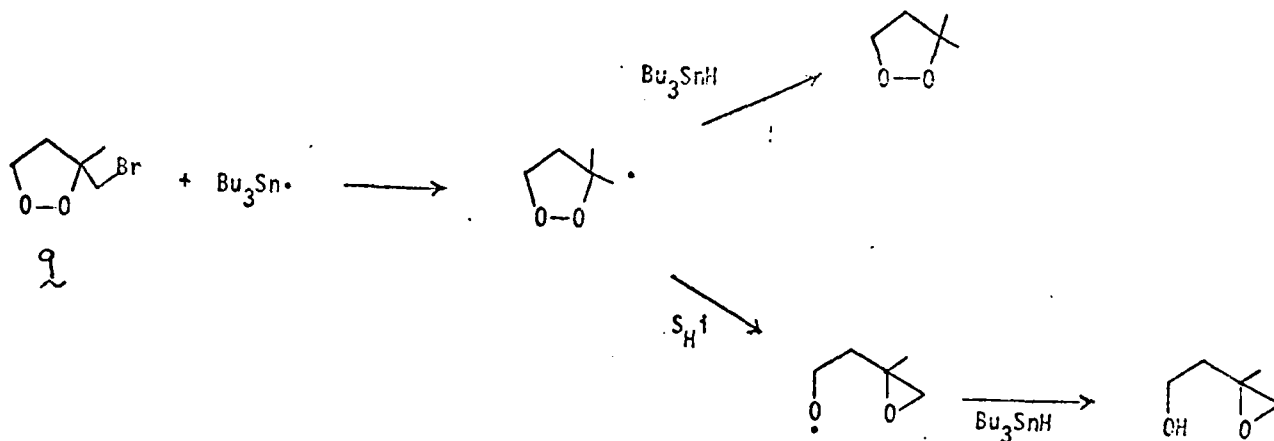
By carrying out reactions with different concentrations of Bu_3Sn-H, the rate constant for S_Hi can be determined. These rate constants, k_{S_Hi}, for a series of radicals are shown below.

-7-

$$k_{S_H i} \ (\text{sec}^{-1})$$

10   1×10^4

11   8.7×10^5

12   7.5×10^4

13   < 1

14   1.2×10^4

15   < 10

Rate constants for $k_{S_H i}$ range generally from 10^4-10^6 sec^{-1} for the series of radic
radicals 10-15 with two exceptions, radicals 13 and 15. In both of those species, the attacking radical cannot approach the peroxide bond with $\phi \approx$ 180° because of geometric constraints. In 13, for example, the angle ϕ is 100° at a maximum while in radical 15, the radical center is fixed with $\phi \approx$ 60°. Note that the epimeric radical to 15, 14 (which has equitorial substitution and $\phi \approx$ 180), has a "normal" $k_{S_H i}$.

13
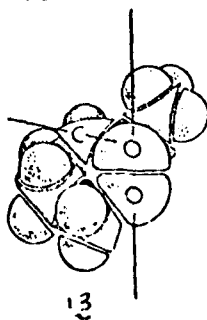
We conclude from these studies that radical substitution on the peroxide bond does, indeed, follow a colinear approach pathway. The $S_H 2$ and $S_N 2$ pathways for reaction on first-row elements are thus apparently similar, with back-side displacement being the rule.

c.) List of Publications

"The Chemistry of Cyclic Peroxides: The Formation and Decomposition of
      Prostaglandin Endoperoxide Analogs", Ned A. Porter, John R. Nixon, and
      Dennis W. Gilmore, Organic Free Radicals, ed., William A. Pryor,
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"Cyclic Peroxides by Intramolecular Peroxymercuration of Unsaturated
      Hydroperoxides", J. R. Nixon, M. A. Cudd and N. A. Porter, J. Org.
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"Separation and Purification of Lecithins by High Pressure Liquid
      Chromatography, N. A. Porter, R. A. Wolf, and J. R. Nixon, Lipids, 14,
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"Synthesis of Prostaglandin H ", Ned A. Porter, Jim D. Byers, Katherine M.
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"The Preparation and Purification of Arachidonic Acid Hydroperoxides of
      Biological Importance". Ned A. Porter, James Logan, Voula
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"The Autoxidation of Arachidnic Acid: Formation of the Proposed SRS-A
      Intermediate", Ned A. Porter, Richard A. Wolf, Elizabeth M. Yarbro,
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"A Fixed Geometry Study of the S 2 Reaction on the Peroxide Bond", Ned A.
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"Prostaglandin G_2", Ned A. Porter, Jim D. Byers, A. E. Ali, and Thomas A.
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"The Free Radical Oxidation of Polyunsaturated Lecithins", Ned A. Porter,
      Richard A. Wolf, and Hugo Weenen, Lipids, 15, 163(1980).

"A New Route to Lipid Hydroperoxides: Orbital Symmetry Controlled Ring
      Opening of Vinylcyclopropyl Bromides", Ned A. Porter, David H.
      Roberts, and Carl B. Ziegler, Jr., J. Amer. Chem. Soc., 102,
      5912(1980).

"The Autoxidation of Poly-Unsaturated Lipids: Factors Controlling the
      Stereochemistry of Product Hydroperoxides", Ned A. Porter, Bruce A.
      Weber, Hugo Weenen and Jamil A. Khan, J. Amer. Chem. Soc., 102,
      5597(1980).

"Serial Cyclization of Peroxy Free Radicals: Models for Polyolefin
      Oxidation", Ned A. Porter, A. Nicholas Roe, and Andrew T. McPhail,
      J. Amer. Chem. Soc., 102, 5912(1980).

d.) List of Participating Personnel

		Ph.D. earned
M. Amelia Cudd	graduate student	1980
A. Nicholas Roe	graduate student	--
James Logan	graduate student	--
Carl B. Ziegler, Jr.	graduate student	1981
David Roberts	graduate student	--